

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Rudolf Eckardt et al.

Serial No. 09/447,490

Filed on 11/23/99



GAU 1624
Examiner: T. McKenzie

For A PROCESS FOR PRODUCING CARBAMAZEPINE

Attorney's Docket 0691-018a

Box Appeal
Hon. Commissioner of Patents and Trademarks
Washington DC 20231

Sir:

SUBSTITUTE BRIEF ON APPEAL

This Substitute Brief on Appeal is enclosed in triplicate. A hearing was already previously requested and the requisite fees were paid. An appeal conference was already requested.

This Substitute Brief on Appeal is being filed in response to the notice of deficiencies of compliance of the original Brief on Appeal with certain formal requirements (missing headings) of Rule 37 C.F.R. 1.192, mailed on September 7, 2000.

1. Real party in interest.

The assignee of the above-identified application is Arzneimittelwerk Dresden GmbH, a subsidiary of Asta-Medica GmbH, which in turn is a subsidiary of Deutsche Gold-und-Silberanstalt, all German corporations.

2. Related appeals.

This application was previously appealed under Appeal No. 1996-1528, and the present appeal is based on an amended claim from the earlier case of the earlier appeal. Applicant is not aware of any other appeals or interferences that would have a bearing on this appeal.

3. Status of claims.

Claims 2-9 of the application that are on appeal, are reproduced in the Appendix hereto.

Original claim 1 was replaced by claim 8. Claim 6 was indicated as allowable if rewritten in independent form. As shown under the next heading the allowable new

claim 9 is claim 6 is now rewritten in independent form and is therefore not being appealed.

4. Status of amendments.

The examiner's objection to the word "optionally" was complied with by its deletion from claim 8 after final rejection, as having been unnecessary. New claim 9 is not on appeal; it was deemed by the examiner to be allowable.

5. Summary of invention.

The principal claim (claim 8) recites a **single step process** for producing carbamazepine by reacting iminostilbene with an alkali cyanate in an acidic medium **consisting of acetic acid** (or a mixture of acetic acid with water (3/13), or with alcohol (3/13)). The parenthetical numbers in the foregoing sentence indicate the page and line Nos. of the disclosure where each of those is mentioned for the first time. As it is well known, even the most concentrated form of acetic acid contains a substantial amount of water. The herein claimed process produces an excellent yield of the carbamazepine end product in the order of 98%, without the need to employ any protective measures against toxic gases.

6. Issues.

The two issues in the appeal are that (1) the claims of the reference (on which the rejection is based) recite an entirely different reaction than the claims on appeal; and (2) the reference teaches the opposite of what is asserted by the examiner as the basis of the rejection. These two issues were repeatedly pointed out but were steadfastly ignored by the examiner.

The rejection, which is an entirely different rejection than on which the earlier appeal was predicated (since here acetic acid is now **expressly** specified as being the sole acid that is present in the single step process of the present claims), is based on European patent No. 277,095 (Acklin et al.). It is expressly **not** based on the US counterpart of Acklin et al. (U.S. patent No. 4,847,374), because the rejection is based on the German language **claims** of the European patent. Apparently the examiner was unable to find a basis in the disclosure of Acklin et al. on which to base the rejection. The claims of Acklin et al., on which the rejection of the present single step process is based, are directed to the second step of the two-step reaction of Acklin et al. in which carbamazepine is produced from a corresponding N,N-(dibenzohexatriethylene)amine by a reaction with cyanic acid (claim 1 of Acklin et al.), in an organic solvent in the presence of an acidic agent (claim 2), wherein both the solvent and the acidic agent are acetic acid (claim 14). In the first step of the 2-step reaction of Acklin et al. (which is not contained in its aforementioned claims on which the rejection is based, the cyanic acid used in the claimed second step is obtained by liberating the cyanic acid in reaction of an acid **that has to be stronger than acetic acid**, with an alkali cyanate, because acetic acid is **expressly** (according to Acklin et al.) not capable of liberating

cyanic acid from its salts (e.g. alkali cyanates such as are used in the present invention).

As no accurate translation of Acklin et al. is available, but only a critique of an earlier, erroneous translation, claims 1, 2 and 14 of Acklin et al. read in translation:

“1. A process for producing of N, N-(dibenzohexatriethylene) ureas, characterized in that reacting a corresponding N, N-(dibenzohexatriethylene) amine with cyanic acid).

2. A process according to claim 1, characterized in that the reaction is carried out in an organic solvent or mixture of organic solvents in the presence of an acidic agent.

14. A process according to claims 2-4 and 8, characterized in that the acidic agent and also the solvent is acetic acid.”

7. Grouping of claims.

The claims on appeal are in a single group that stands together.

8. Argument.

The present claims on appeal recite a single step process which is a **reaction between only:**

1. **An alkali cyanate,**
2. iminostilbene, and
3. acetic acid, and **nothing else.**

In contrast, the second, single step of the two step reaction of the claims of Acklin et al. on which the rejection is based, is not reacting an alkali cyanate with iminostilbene and acetic acid, but it reacts:

- a. **cyanic acid** with
- b. iminostilbene in the presence of acetic acid as a solvent and an excess, catalytic amount of acetic acid as the acidic agent.

Acklin et al. describes obtaining the cyanic acid by liberating it with an acid that is a stronger acid than acetic acid (e.g. formic acid) from a cyanate salt, because acetic acid is not strong enough to accomplish that.

The reactions of the claims of Acklin et al. and of the claims on appeal. **are between entirely different reaction partners.** The examiner has entirely ignored the fact that was repeatedly emphasized by the applicant, that **no cyanic acid (i.e. hydrogen cyanate) is involved in the herein claimed process.** There is no cyanic acid present, not only because the claims expressly provide that the sole acid that is present in the herein claimed reaction is acetic acid, but also, because cyanic acid is a highly toxic gas, and therefore any reaction in which it is involved has to be carried out under special

protective conditions against toxic gases, i.e. sealed from the ambient atmosphere. Therefore, the reaction of the claims of Acklin et al. that is relied on for the rejection, is an entirely different reaction between entirely different reaction partners than the reaction claimed in the present invention.

The present invention does not only dispense with the use of the toxic cyanic acid, because no ambient protection is required, but **Acklin et al. actually teaches away** from the possibility of the presence of cyanic acid under the conditions of the herein claimed reaction. Per the teaching of Acklin et al. **it is impossible for cyanic acid to be present in the herein claimed reaction.** That is because the disclosure of Acklin et al. describes the conditions under which the cyanic acid can be obtained in a first step, before it is used in its claimed reaction as a second step of a two step reaction. In that first step Acklin et al. obtains the cyanic acid by reacting an alkali cyanate with an acid that is a sufficiently strong acid to liberate cyanic acid from, its salts. Acklin et al uses formic acid or an acid that is at least as strong an acid as formic acid, because Acklin et al. teaches that **an acid that is weaker than formic acid, e.g. acetic acid, is not capable of liberating cyanic acid from its salts.** This is the reason that **Acklin et al. actually teaches away from the present invention,** because since in the process of the present invention acetic acid is the sole acid that is employed, and therefore, according to the teaching of Acklin et al. **no cyanic acid can be formed in the presently claimed reaction.**

There is yet further evidence that Acklin et al. does not recognize, or have any bearing on the presently claimed process. Claims 22-24 of Acklin et al. are directed to the two-step process of Acklin et al., rather than only to the second step on which the current rejection is predicated. In claims 22-24 iminostilbene is reacted with an alkali cyanate in the presence of acetic acid, but Acklin et al. finds it necessary **also to include a from 5% to 40% excess of sulfuric acid.** This is further clear evidence that Acklin et al. concluded that acetic acid alone is insufficiently strong to produce the cyanic acid which it requires to produce the end product, and a further, a stronger acid such as sulfuric acid, even an excess of sulfuric acid, is also required. The claims on appeal are restricted to acetic acid being the sole acid that is present in the reaction, and Acklin et al. teaches away from this, because it maintains that the herein claimed reaction cannot work. In the claims on appeal neither cyanic acid, sulfuric acid, nor any other acid outside of the acetic acid is present and all of these unneeded further acids are thus expressly excluded, and the reaction works by producing a yield in the order of 98%.

Thus the present invention uses an entirely different reaction than that which takes place in Acklin et al.

Consequently, there are "only" two problems with the outstanding rejection, which were **repeatedly** ignored by the examiner:

- 1.) the reactions in the reference and in the appealed claims are entirely different, because critically different reaction partners are involved, and
- 2.) the reference teaches the opposite of what is asserted by the examiner as the basis of the rejection.

These facts do not appear to hinder the examiner from incorrectly maintaining (without any basis in fact or in law) that cyanic acid is used in the reaction of the presently claimed process. In fact, nothing seems to be able to stand in the way of the examiner maintaining the outstanding rejection, be they facts or even the law. The rejection is based entirely on fiction - science fiction.

In carrying forward its line of contradicting the teachings of Acklin et al., the examiner creates some extremely speculative, scientifically sounding theorizing that is entirely unwarranted from, and contradictory to, Acklin et al., as well as to the presently claimed process. The examiner's unwarranted, theorizing speculation about the formation of cyanic acid with acetic acid as the sole acid is highly and unrealistically unlikely, not only because it contradicts the teaching of Acklin et al, but also because acetic acid is not only a weaker acid than formic acid, but **acetic acid is also a weaker acid than cyanic acid which it, therefore, cannot liberate from its salts**¹. Even if in the case of slight equilibrium distortions one might speculate about the formation of minimal amounts of cyanic acid, the facts that (i) no formation of the any of the highly toxic, lachrimating kind of cyanic acid is being sensed, and (ii) the reaction in the case of the present invention goes forward with a yield in the order of 98%, bespeaks the presence of any cyanic acid, and certainly not any meaningful amount thereof.

For the above reasons, the applicant will not even try to deal any further with the examiner's speculations, except to point to its irrelevancy and contradictory nature to the baseline that has to be considered - that drawn between at one extreme the reference and at its other extreme the present invention. There is no room along that baseline for excursions into irrelevant asides.

The examiner's unsupported speculations (which also contradict the teachings of the sole reference Acklin et al.), have no probative value whatsoever. They were challenged before, and are challenged herewith again, and the only way to turn those speculations into evidence, for what they are worth, is to submit the same with an examiner's affidavit pursuant to 37 C.F.R. 1.104(d)(2).

¹The pKa value of trichloroacetic acid, a very strong acid, is 0.70. The pKa value of cyanic acid is 3.47, and of formic acid is 3.77. Acetic acid is the weakest of them all at 4.75.

The examiner stated in Paper No. 8 that a new translation of Acklin et al. has been ordered. No copy of any new translation was received by the undersigned, but only of the critique of the original, erroneous translation. The examiner maintains that Acklin et al. mentions acetic acid in column 3, lines 27-41. If the examiner maintains that that mention of acetic acid means that it alone can liberate cyanic acid from its salts, the examiner is seriously mistaken and has completely misread Acklin et al.

That reference discusses in column 2, lines 39-54 that only certain protonic acids are sufficiently strong to liberate cyanic acid from its salts. Thus, it lists, mineral acids such as sulfuric acid, organic carbonic acids such as trichloroacetic acid, the acid strength of the acids used to correspond **at least** to that of formic acid (see footnote).

After line 55 and bridging over to column 3, Acklin et al. introduces the concept of a **further** "acidic agent" as a reaction-accelerating catalyst (for the second step of the reaction as an adjunct or alternative to heating), in addition to the acid used to liberate the cyanic acid from its salts. That acidic agent is present only in a minimal, catalytic amount, and if desired may be also a small excess of the acid that is used to liberate the cyanic acid from its salts. The examiner overlooks that part of Acklin et al. from line 55, and mistakenly relies only on the part of Acklin et al, from column 3, line 27. In column 3 lines 27-41 Acklin et al, refers to the presence of acetic acid, but Acklin et al. does that only in reference to the catalytic amount of the "acidic agent" **but not with reference to the acid used to liberate cyanic acid from its salts.** The "acidic agent" is only the infinitesimally small, the catalytic amount of additional acid, and therefore, when acetic acid is mentioned as a possible acidic agent that refers only to the small amount of additional acid catalyst for the second reaction step of Acklin et al, namely the reaction of the cyanic acid with the iminostilbene. Acetic acid may also be employed as a solvent, but in view of what has been stated in Acklin et al. earlier about the need for a stronger acid, it cannot be used according to Acklin et al. under any circumstances to liberate cyanic acid from its salts,

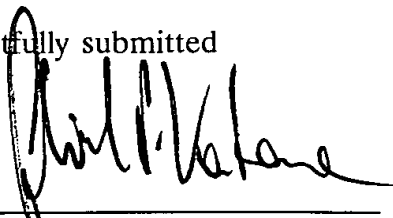
There was a further rejection on the basis of alleged new matter. The rejection was responded to, and it is not clear whether that rejection was settled, or whether it is continuing. Therefore, the applicant prophylactically re-presents the earlier argument that was presented against it. The rejection objected to the inclusion in claim 8 of "aqueous alcohol." As it was pointed out during the prosecution, the original claim has specified "aqueous acetic acid" (which means acetic acid and water). Furthermore, as has already been pointed out above, all forms of acetic acid do contain substantial amounts of water. The original claim also specified "with water or alcohol" (which means aqueous acetic acid either with more water or with just the original amount of water, and alcohol). Accordingly, either of these terms includes acetic acid, water and alcohol as one alternative to aqueous acetic acid with alcohol, i.e. acetic acid, water, and alcohol, i.e. aqueous alcohol. Hence the later added term of "aqueous alcohol" cannot, and does not represent any new matter., as water, acetic acid and alcohol were

cannot, and does not represent any new matter., as water, acetic acid and alcohol were simultaneously present as ingredients of the original claims. The objected term can however be easily removed if the objection were to continue through the appeal.

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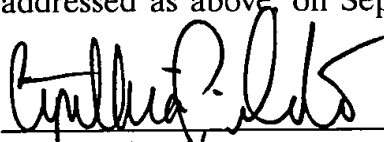
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Respectfully submitted



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I hereby certify that this correspondence is deposited with the U.S. Postal Service, addressed as above, on September 28, 2000



Cynthia A. Pilato

Appendix

8. A process for producing carbamazepine, which comprises reacting iminostilbene with an alkali cyanate in an acidic medium consisting of acetic acid, or a mixture of acetic acid with water, or with alcohol, or with an aqueous alcohol, and recovering the resulting carbamazepine.

2. The process of claim 8 wherein an aqueous acetic acid mixture is employed containing up to about 20% wt. water based on the mixture.

3. The process of claim 8, wherein an alcoholic acetic acid mixture is used containing up to about 10% wt. alcohol based on the mixture.

4. The process of claim 3, wherein the alcohol is methanol or ethanol.

5. The process of claim 8 wherein the alkali cyanate is gradually added directly to the reaction mixture of iminostilbene and acetic acid, or acetic acid mixture.

6. The process of claim 8 wherein the alkali cyanate is added in an aqueous solution.

7. The process of claim 8 wherein the alkali cyanate is sodium- or potassium cyanate.

9. (Stated to be allowable) A process for producing carbamazepine, which comprises reacting iminostilbene with an alkali cyanate in an aqueous solution, said reacting being carried out in an acidic medium consisting of acetic acid, or a mixture of acetic acid with water, or with alcohol, or with an aqueous alcohol, and recovering the resulting carbamazepine.